Treatment of Vertebral Artery Origin Stenosis with a Pharos Stent Device: a Single Center Experience

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Summary

Atherosclerotic stenosis of vertebral artery (VA) origin exceeding 70% severity accounts for one third of all vertebrobasilar strokes. For a period of one year the results of endovascular treatment of VA stenosis with the new Pharos stent device were assessed.

Twenty-two patients with symptomatic VA stenosis were treated with the Pharos stent. Clinical status and stenosis grade were documented before treatment and 24 hours, one, three and twelve months after treatment via ultrasound and magnetic resonance tomography.

All procedures proved to be technically successful without the occurrence of intra-procedural complications. During the observation period of more than one year, 55% of patients were documented with a mean stenosis degree of 60%: two (10%) of these patients showed a residual stenosis after angioplasty and nine patients (45%) an in-stent restenosis, whereas only two patients were documented with a hemodynamically relevant in-stent restenosis of 80%. These two patients were retreated with balloon dilatation. None of the patients showed neurological deterioration or new abnormalities at magnetic resonance tomography examination. Neither VA occlusion nor restenosis of the contralateral VA negatively affected the clinical outcome. An in-stent restenosis was developed by more female than male patients.

VA origin stenting with the Pharos stent device is an effective treatment of stenosis. The good clinical results compared to the high restenosis rates have to be examined in further studies. Pin particular, it has to be determined whether the Pharos stent allows the vessel time for collateralization, whether double antiplatelet treatment prevents recurrent cerebrovascular events or whether merely the low restenosis degree is causative for the clinical outcome.

Introduction

Stroke is the leading cause of death and disability worldwide [1]. Approximately 25% of ischemic strokes involve the vertebrobasilar circulation [2,3].

Stenosis or occlusion involving vertebral artery (VA) origin is a significant cause of posterior circulation stroke and can result from either arterial embolus or hypoperfusion, or both [4].

Secondary prevention aims to improve the hemodynamic situation and intends to eliminate possible sources of thromboembolism. Primary treatment of stenosis of VA involves medical management in combination with a reduction of risk factors. When medical treatment fails, endovascular treatment of VA stenosis with percutaneous transluminal balloon angioplasty with or without stent implantation is an alternative to surgery. The CAVATAS (carotid and VA transluminal angioplasty study) trial showed that angioplasty and/or stenting of VA ostial stenosis was feasible but showed a high restenosis rate [5].

Twenty-two patients with stenosis of VA origin were treated with the Pharos stent device in a single-center and were monitored during one year after treatment.

Materials and Methods

Patient population

All consecutive patients suffering from VA origin stenosis who were treated with a Pharos stent in the years 2008 and 2009 were included in this study.

Demographic data, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS) score [6] at admission, discharge and follow-up, as well as the modified Ranking Scale (mRS) at admission, discharge and follow-up were assessed by stroke neurologists.

The following stroke risk factors were evaluated: age, sex, hypertension, atrial fibrillation, hyperlipidemia, diabetes, current smoking, peripheral arterial occlusive disease (PAOD) and coronary artery disease.

Diagnosis of posterior circulation stroke was based on sudden onset of focal neurological deficits from the vertebrobasilar territory lasting more than 24 hours with corresponding findings in brain imaging. Symptoms of the vertebrobasilar territory passing within 24 hours were defined as severe transient ischemic attacks (TIA). Vertebrobasilar insufficiency was defined through symptoms of vertigo, dizziness and nausea.

Brain imaging involved non-enhanced and enhanced computed tomography (CT scan and CT angiography) and magnetic resonance tomography imaging (MRI).

The diagnosis of proximal VA stenosis was established by color-coded duplex ultrasonography in all patients and verified via CT angiography or contrast enhanced MRI. Hemodynamically significant ostial stenosis was suspected if ultrasound revealed peak systolic velocities > 230 cm/s at the origin of the VA [7].

Indications for stenting

Patients treated were considered to be at high risk of further strokes by both, vascular neurologists and neurointerventionalists at the neurological department where the patients were hospitalized.

Only patients with a documented posterior circulation stroke, severe TIA or vertebrobasilar insufficiency symptoms and corresponding VA origin stenosis (VAOS) were selected. These patients fulfilled the criteria for symptomatic VAOS. In patients with vertebrobasilar insufficiency symptoms, the VAOS had to match the vascular cerebral lesions.

Treated patients with stent angioplasty, had to meet further conditions: angiographically verified symptomatic VAOS of more than 70% and a hypoplastic contralateral VA (defined as a diameter below 2 mm) or stenosis of more than 60% and a contralateral occluded VA.

Patients with an additional intracranial stenosis in the vertebrobasilar territory, hemodynamic relevant carotid stenosis, or patients with a cardioembolic stroke etiology were excluded from this study.

Treatment

All patients were treated electively and received a combined antiplatelet medication consisting of 100 mg acetylsalicylic acid (ASA) and 75 mg clopidogrel for at least ten days after implantation of the Pharos stent, a hybrid cell design device of cobalt chromium.

A platelet function analyzer (Multiplate® analyser Dynabyte Medical, Munich, Germany) was used for platelet function assessment of the response to ASA and clopidogrel [8]. Only patients documented with drug levels within the therapeutic range underwent stent angioplasty.

All implantations were performed under general anaesthesia. Patients received 5000IE heparin at the beginning of the procedure. In general, a transfemoral approach was applied; only in one patient was a transbrachial approach used. After diagnostic angiograms including a 3D rotational angiogram for exact measurement of the residual lumen, the length of the stenosis and the diameter of the adjacent non-stenotic segment of the vertebral artery were defined. A coaxial system consisting of a long 6F sheath and a 6F guiding catheter, or just a 6F guiding catheter alone, was placed in the subclavian artery. Stent dimensions were selected according to the 3D rotational angiogram data. The dimensions chosen were just long enough to cover the entire plaque and to have a diameter corresponding to the adjacent non-stenotic segment of the vertebral artery in order to avoid overexpansion. The Pharos stent was inserted via a hydrophilic neuroradiological microguidewire (Transend EX 14; Boston

Scientific, Natick, MA, USA). Under roadmap guidance, the stenosis was passed with the microguidewire followed by the stent. After correct positioning, the stent was deployed with pressure applied according to the compliance chart of the manufacturer. The maximum balloon size was 20%. The objective was to slightly underdilate the stenosis and not to exceed the diameter of the adjacent artery. The balloon was inflated and deflated slowly over a period of one minute and control angiograms were performed before retrieval of the deflated balloon to check for adequate recanalization, stent position and local complications. Overall, protection devices were not used during the stenting. After retraction of the stent delivery catheter, control angiograms of the entire territory of the stented artery were performed in two orthogonal projections. Angio-Seal, an anchor-collagen closure device for the artery access was used for controlled deployment [9].

After the procedure, all patients received daily oral double antiplatelet therapy for three months and then started a lifelong regimen of 100 mg per day of oral ASA.

Clinical and radiological follow-up

After the procedure, the patients were monitored at the neurological stroke unit for 24 h. Clinical and radiological follow-ups were scheduled for one, three and 12 months after the procedure.

Duplex ultrasound to evaluate stent patency was performed during each follow-up and the platelet function was evaluated. DSA was performed in patients who showed significant restenosis at the ultrasound examination. Cranial MRI was performed on a regular basis – immediately before discharge, after a period of three months and subsequently again after one year.

Results

22 patients (14 males – 63.6%, 8 females – 36.4%) were treated with a Pharos stent for a high grade symptomatic VAOS. The age of patients ranged from 51 to 84 years (mean 69.3). The mean angiographic VA stenosis degree before stenting was 81.8% (range: 70-90%). Patients received double antiplatelet therapy before stent angioplasty with a mean medication time of ASA 17 days and clopidogrel 22 days.

59.1% (13/22) had left-sided VAOS and 40.2% (9/22) a right-sided VAOS. 9.1% (2/22) had a stenosis of the contralateral VA, with a mean stenosis grade of 55%, in 31.8% (7/22) the other VA was hypoplastic. 27.3 % (6/22) showed an occlusion of the other VA. (Table 1)

Patients suffered from either posterior circulation strokes (63.6% - 14/22), severe TIAs in the posterior circulation (18.2% - 4/22), or showed vertebrobasilar insufficiency symptoms (18.2% - 4/22). On admission, the mean mRS of all patients (including strokes, TIAs and vertebrobasilar insufficiency symptoms) was 1.9 and at discharge 0.7. The mean NIHSS was 3.7 at admission and 0.7 at time of discharge. One year after the procedure, all patients showed an improvement of symptoms with a mean mRS of 0 and a mean NIHSS of 0.5.

The MRI analysis showed microangiopathic changes in all patients. 36.4% of the patients additionally had acute ischemic lesions and 13.6% showed chronic lesions.

The risk factors were analyzed accurately: 73% (16/22) of patients were documented with hypercholesterolemia, 18% (4/22) with diabetes, 18% (4/22) with atrial fibrillation, 64% (14/22) with high blood pressure, 45% (10/22) with coronary artery disease, 0% with peripheral arterial occlusive disease and 18% (4/22) with current nicotine abuse.

The multiplate testing for all patients showed levels within the therapeutic range before stent placement and at all follow-ups. An overview of the main results is given in Table 1.

Immediate angiographic results and complications

The technical success rate of stent placement was 100%. Three patients required placement of two stents simultaneously.

There was no case of in-stent thrombosis at the time of completion of the procedure.

The patient with the transbrachial approach developed an arterial embolism of the right brachial artery and underwent embolectomy.

Radiological and clinical follow-up 24-hour follow-up

After 24 hours, none of the patients was documented with an in-stent restenosis. One patient was documented with a mean velocity of 200 cm/s as measured by ultrasound, which is equivalent to a residual stenosis. This patient suffered from breast carcinoma with general

Table 1 **Clinical Summary of 22 patients undergoing vertebral artery stenting.**

	Age/ Sex	Presenting symptoms	VA Stent	VA	MRS - admission	MRS - discharge	NIHSS - admission	NIHSS - discharge	Pharos stent diameter/length	vessel diameter (mm)	contralateral VA	Carotid stenosis	
												RIGHT	LEFT
1	63/m	Cerebellar infarction	L	80%	4	1	10	1	3.0 × 13	3.2	hypoplasia	50%	30%
2	81/m	TIA	L	80%	0	0	0	0	4.0 × 13	4.1	occlusion	TEA	occlusion
3	79/m	Brainstem infarction	L	80%	1	0	0	0	3.5 × 13	3.6	hypoplasia	STENT	40%
4	65/m	VBI	L	80%	0	0	0	0	4.0 × 13	4.2	occlusion	0%	0%
5	64/f	Cerebellar infarction	R	90%	1	1	8	1	4.0 × 8	4.1	hypoplasia	50%	20%
6	69/f	Pons infarction	R	90%	1	3	12	1	4.0 × 13	3.9	hypoplasia	30%	20%
7	68/m	Cerebellar infarction	R	70%	1	1	4	1	4.0 × 8	4.1	occlusion	STENT	20%
8	69/m	Cerebellar infarction	L	90%	1	1	4	2	3.5 × 8	3.7	hypoplasia	20%	50%
9	60/f	Posterior infarction	L	90%	1	0	6	1	3.0 × 8	3.1	hypoplasia	0%	0%
10	75/f	Cerebellar infarction	L	90%	1	1	8	2	3.0 × 8	3.1	hypoplasia	40%	20%
11	79/m	Cerebellar infarction	L	80%	1	0	3	0	4.0 × 13	4.1	occlusion	30%	30%
12	57/m	VBI	R	80%	0	0	0	0	3.0 × 13	3.2	hypoplasia	0%	0%
13	79/m	Cerebellar infarction	R	80%	1	1	8	1	3.5 × 8	3.6	hypoplasia	50%	20%
14	84/m	TIA	R	90%	0	3	1	1	2.75 × 10	2.9	hypoplasia	30%	30%
15	57/f	Brainstem infarction	L	90%	1	1	4	0	4.0 × 13	4.2	50%	10%	10%
16	82/f	VBI	R	90%	0	0	0	0	3.0 × 13	2.9	hypoplasia	50%	50%
17	67/m	TIA	L	70%	0	0	0	0	3.5 × 13	3.6	occlusion	occlusion	20%
18	73/f	VBI	R	80%	0	1	0	1	3.0 × 8	3.2	hypoplasia	0%	0%
19	53/f	Cerebellar infarction	L	70%	1	1	2	1	3.5 × 8	3.6	hypoplasia	10%	10%
20	58/m	Brainstem infarction	R	80%	1	0	4	0	3.75 × 8	3.8	occlusion	30%	30%
21	82/m	TIA	L	70%	0	0	6	0	2.5 × 10	2.6	60%	50%	0%
22	51/m	Cerebellar infarction	L	80%	1	1	2	1	3.0 × 13	3.2	hypoplasia	20%	20%

metastasis, but without cerebral metastasis and showed no neurological deficit.

None of the 22 patients suffered from a new stroke after the procedure, although one (4.5%, 1/22) showed an asymptomatic new small ischemic infarction in cranial MRI.

One month follow-up

Twenty-one patients were available for the follow-up. The total stenosis rate was 9.5% (2/21). One patient (4.8%) was detected with an in-stent restenosis of 60% measured by ultrasound (mean velocity 120 cm/s) without neurological deficits, the other (4.8%) who was documented with a residual stenosis after 24 hours did not show an increasing velocity in ultrasound and was also clinically asymptomatic.

Combined antiplatelet medication of ASA and clopidogrel was continued. None of the patients showed new neurological deficits.

Three month follow-up

Again, 21 patients were available. The total stenosis rate was 48% (10/21).

Among these patients, one patient (5%) had already been documented with residual stenosis after 24 hours and after one month. 43% (9/21) now showed an in-stent restenosis with a mean stenosis rate of 60% (ranging peak velocities in ultrasound 120 – 200 cm/s).

The ultrasound velocity measurement of the patient previously documented with in-stent restenosis remained unchanged. None of the patients showed new neurological deficits. MRI scans revealed no fresh ischemic cerebral lesion. Combined antiplatelet medication was stopped in all patients and ASA medication was continued.

One year follow-up

A total of 20 patients were available. The total stenosis rate was 55% (11/20). Among these patients, 5% (1/20) were documented with a residual stenosis and 40% (8/20) with an in-stent restenosis. Another two patients (10% - 2/20) showed an occlusion of the previously stented VA. Among the 40% of patients documented with in-stent restenosis, only 10% (2/20) showed a hemodynamically relevant restenosis degree of 80% (ultrasound peak velocity above 200 cm/s). These patients were even retreated with balloon dilatation. One of these two patients developed a VA occlusion and the other patient was documented with a residual stenosis of 60% (peak velocity 120 cm/s) at the follow-up. The other 35% (7/20) of patients were documented with a maximum restenosis degree of 60% (ultrasound peak velocity in between 120 - 150 cm/s). These patients were not retreated. All patients are still free of new neurological symptoms.

Discussion

The discussion whether endovascular treatment is an improvement for patients suffering VAOS or not is ongoing.

The only randomized trial comparing endovascular treatment with medical treatment is the Carotid and VA Transluminal Angioplasty Study (CAVATAS). This trial showed that recurrent stenosis was more common in patients who underwent endovascular treatment than in patients who had endarterectomy [5]. Another study concluded that despite a technical success rate of 97% and a low incidence of complications, VOAS is associated with a high rate of moderate-to-severe restenosis [10].

In balloon angioplasty without stenting, the restenosis rates reported in the literature are very high, even up to 100% [11]. Former studies used bare-metal stents and reported high restenosis rates in the VA of up to 42.9% within six months [12]. More recently, drug eluting stents developed for coronary interventions have been used to treat carotid or VA stenosis. The reported restenosis rate was low, although no long-term results have yet been published [13].

A recent study revealed a decreased in-stent restenosis rate in patients treated with drug eluting stents [14]. Another study investigated an in-stent restenosis in 11 out of 35 patients. Of these patients, 9/24 (38%) treated with a non drug eluting stent and 2/12 (17%) treated with a drug eluting stent developed an in-stent restenosis. The conclusion of this study was that drug eluting stents for treatment of VA origin stenosis may decrease the incidence of restenosis, compared to non drug eluting stents [14].

Due to its silicon carbide coating, the Pharos stent provides an enhanced biocompatibility. However, in our study a total in-stent restenosis rate of 4.8% after one month and 42.9% after three months could be documented. After one year, 45% (n=9/20) showed an in-stent restenosis and 10% (2/20) an in-stent occlusion.

Only a few studies covering the Pharos stent device are currently available. A recent study investigated 32 patients with intracranial stenosis treated with the Pharos stent device. Among these patients, only 8.7% developed an in-stent restenosis of the intracranial artery [15].

Albuquerque et al. highlighted the fact that there is increased elastin and smooth muscle at the vessel lumen in other circulations (coronary and renal). This might explain the poorer response to angioplasty and stenting, with increased in-stent restenosis rates [9]. Other authors stated that the leading cause of in-stent restenosis was intimal hyperplasia [16]. Neointimal hyperplasia develops through the processes of thrombus, deposition, inflammation, smooth muscle cell and fibroblast migration, and cellular proliferation [17].

In our patients, we could observe similar high in-stent restenosis rates as also reported in former studies covering VAOS stenting [9,14,15,18]. But among our patients, in 35 % the mean in-stent restenosis degree was 60% after one year and hemodynamically insignificant. Only two patients with a hemodynamically significant restenosis of 80% were documented and therefore retreated with balloon dilatation.

The high peak velocity of 200 cm/s after 24 hours in one patient might be associated with a breast carcinoma with metastasis. Oncological diseases are described as being a higher risk factor for stent thrombosis, because of the prothrombotic state and the association of chemotherapeutic agents with delayed endothelialization [19,20]. The increased peak velocity however is most likely to be explained as a residual stenosis directly after treatment, as reported in other studies [21].

Former studies reported that VA stenting reduces risk for recurrent posterior circulation strokes or hard TIAs, particularly, in patients who had occlusive diseases of both vertebral arteries [22]. In our patients, we could observe a moderate rate of in-stent-occlusion and high rate in-stent restenosis without neurologically recurrent symptoms. 27.3% had an occlusion of the VA and a stenosis of the other. Three patients were diagnosed with an in-stent restenosis, without clinical deterioration or MRI changes.

There was a high restenosis and in-stent-occlusion rate, although combined antiplatelet medication of ASA and clopidogrel was proven to be efficient through multiplate test system. Wong et al. reported that patients under medical treatment with VAOS were more likely to suffer from a carotid territory stroke and myocardial infarction during follow-up than recurrent vertebrobasilar stroke [23]. This study failed to show any benefit from endovascular treatment of VAOS, but the numbers of patients included in their study was small. The recommendation was to focus on global reduction of vascular risk, including prevention of carotid territory stroke and myocardial infarction, in patients with VAOS [23]. They showed that patients with symptomatic severe VAOS face an 11% annual risk of recurrent posterior circulation stroke or TIA under medical treatment.

In-stent restenosis is said to induce more recurrent cerebrovascular disease in patients after stenting [5]. Surprisingly, we had no symptomatic in-stent restenosis in the patients treated with Pharos stent for VAOS. Even the documented 27.3% who developed in-stent restenosis and had an occluded contralateral VA, were without new neurological deficits at the one year follow-up. We reviewed our control angiograms and could document good collaterals via the posterior communicating arteries and cervical collateral vessels in the patients with an occluded VA and restenosis of the stented other VA, indicating that the hemodynamic stress in the vascular territory of the stenotic vessel had been reduced.

As reported in former studies, combined antiplatelet treatment protects patients from microembolism [24]. Dual antiplatelet treatment may also be responsible for the lack of deterioration in our patients although the average patient developed an instent restenosis or occlusion [25]. Another explanation could be that VA stenting bridges the time, vessels need for developing sufficient collateralization to improve the hemodynamic situation. Furthermore, the combination of antiplatelet therapy and Pharos stenting seems to positively influence the outcome, despite the high restenosis rate. Another important reason for the good clinical outcome of our patient could be that only two patients were recorded with a hemodynamically relevant in-stent restenosis of 80%, the others showed no hemodynamically relevant stenosis degree.

Further analysis is necessary to determine whether dual antiplatelet treatment alone is enough to prevent the occurrence of cerebrovascular events in these patients, or whether vessels do need VA stenting to bridge the time until good collateralization can be achieved.

The limitation of our study was the fact that follow-up angiography of all our patients was

not routinely performed. This may have influenced the analysis and restenosis numbers towards a higher occurrence rate. But because of the good clinical status of all our patients a control angiography was not justified. Further studies that include more patients with longer follow-up periods will be necessary to scientifically prove our theories.

Conclusion

Vertebral artery stenting with the Pharos stent device was shown to be a treatment with acceptable low risks. Despite a high restenosis rate of 55% and an in-stent occlusion rate of 10%, all patients were without new neurological deficit or MRI changes at the follow-ups.

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